Dynamic prognostic nutritional index could be a novel predictor of survival in lung cancer patients treated with nivolumab

Survival predictor of nivolumab: Dynamic PNI change

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Only a part of this article (NLR and DNLR) was presented as poster presentation at the Seventh Turkish Society of Medical Oncology Congress (21–25 March 2018).

Abstract

Aim: Nivolumab, a fully human IgG4 programmed death 1 (PD-1) immune-checkpoint inhibitor antibody, restores antitumor antibody-disrupting PD-1-mediated signaling. Although it has a striking antitumor efficacy, factors predicting response, especially at the beginning of the immunotherapy are important owing to its side-effect profile and high cost. In this study, we aimed to evaluate the predictive value of the neutrophil-lymphocyte ratio (NLR), derived NLR (dNLR), prognostic nutritional index (PNI), carcinoembryonic antigen (CEA) and change of these parameters during nivolumab treatment in patients with non-small cell lung cancer (NSCLC).

Materials and Methods: A total of twenty NSCLC patients were divided into groups with a cut-off basal median NLR, dNLR, PNI and CEA value of 2.9, 1.9, 35, 40.4, retrospectively. NLR, dNLR, and PNI changes were determined at the third cycle of treatment. Basal values and changes in four parameters and the association with clinicopathologic characteristics were analyzed to determine their prognostic values using the Kaplan-Meier method and the multivariate Cox regression analysis.

Results: High pre-treatment NLR, CEA, and low PNI levels were associated with decreased OS and PFS, but high dNLR was associated only with shorter OS. Patients with decreased dNLR at the third cycle had longer OS but increased PNI had longer PFS and OS. In univariate analyses, NLR, dNLR, CEA, PNI and PNI changes were found to be prognostic for OS. However, in multivariate analyses, only PNI change (increase) was found to be independent factors for OS.

Discussion: Increased PNI at the third cycle was found to be the unique predictive factor for OS in cases with NSCLC treated with nivolumab.

Keywords

Nivolumab; Carcinoma; Non-Small-Cell Lung; Immunotherapy; Inflammation; Derived Neutrophil-Lymphocyte Ratio; Nutrition assessment; Prognostic nutritional index; Carcinoembryonic antigen

Introduction

Lung cancer is the most common cause of cancer-related deaths in the United States and 85% of the cases have Non-Small Cell Lung Cancer (NSCLC) [1]. About 50% of these cases presented in the metastatic stage and 5-year OS rates are 1-2%. Fortunately, the OS rates have been found to be increased as high as 13-15% with tyrosine kinase inhibitors and immune checkpoint inhibitors (ICI) [2-3]. Nivolumab is a programmed death 1 (PD-1) blocker antibody belonging to IgG4 family and has been approved as second-line treatment in NSCLC. However, the cost of ICIs are high, and the overall objective response rate with a single-agent ICI in lung cancer is between 20% and 29%; 5-year survival rate of patients treated with nivolumab is approximately 15-16% [4-5]. For these reasons, we need predictive factors for PFS and OS in cases treated with ICI. Tumour-infiltrating lymphocytes, T-cell receptor clonality, tumor mutation burden, and some peripheral blood markers have been found to be predictive for some ICIs including nivolumab, pembrolizumab, and atezolizumab [6]. Eastern Cooperative Oncology Group (ECOG) performance status (PS), lactate dehydrogenase (LDH) level, carcinoembryonic antigen (CEA) level and inflammatory markers such as neutrophil-lymphocyte ratio (NLR) and derived neutrophil-lymphocyte ratio (dNLR) are valuable parameters to determine the response to ICIs [7]. Prognostic nutritional index (PNI) is another inflammatory marker and at the beginning, it has been proposed as a predictive marker for postoperative mortality in cases with gastric cancer [8]. In recent times, its prognostic value has been shown in various cancers including lung cancer. Here we wanted to determine the predictive value of NLR, DNLR, PNI, and CEA for response and PFS/OS times in cases with NSCLC treated with nivolumab.

Material and Methods

Twenty patients with NSCLC treated with nivolumab every 2 weeks after disease progression following platinum-based chemotherapy in Cukurova University, Faculty of Medicine, Department of Medical Oncology between August 2015 and March 2019 were included in the study. The patients in this retrospective study had been registered in an expanded access program, and written consent was obtained from all patients. Nivolumab was continued until progression and/or toxicity was observed.

Inclusion criteria: Twenty cases with NSCLC confirmed by stage IV biopsy, PS 0–2, adequate hematologic, hepatic and renal function, older than 18 years and showing progression after platinum-containing regimens.

Exclusion criteria: Patients with chronic steroid use, cerebral metastatic disease, and having undergone radiation in the last month were excluded.

Patient baseline demographic characteristics were recorded and leukocyte, neutrophil, lymphocyte, platelet counts and albumin, CEA levels were obtained at baseline and before each treatment cycle from hospital operating system. Following formulae were used to calculate NLR, dNLR, ΔNLR, ΔdNLR, and ΔPNI:

NLR: peripheral blood neutrophil count/peripheral blood lymphocyte count

dNLR: peripheral blood neutrophil count/peripheral blood white blood cell count – peripheral blood neutrophil count

PNI: (10 × albumin (g/L) + (0.005 × total lymphocyte count)

ΔNLR: NLR change between the first and the third cycle.

ΔDNLR: DNLR change between the first and the third cycle.

ΔPNI: PNI change between the first and the third cycle.

CEA normal limits: 0–3 ng/mL.

Tumour response was evaluated based on the Response Evaluation Criteria in Solid Tumours (RECIST version 1.1) criteria in every six cycles of nivolumab.

All procedures performed in our study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Statistics

Overall survival (OS) was calculated from the initiation of nivolumab to death and censored at the date of the last follow-up for survivors. Progression-free survival (PFS) was calculated from initiation of nivolumab to date of recurrence or death and censored at the date of the last follow-up for survivors without recurrence. The cut-off values were determined at median levels due to the distribution of the NLR, dNLR, PNI and CEA parameters and a small number of patients. The patients were stratified by NLR ≥2.9 vs. <2.9, dNLR ≥1.9 vs. <1.9, PNI ≥35 vs. <35 and CEA level ≥40.4 vs. <40.4. The association between clinical characteristics and our parameters with OS and PFS were analyzed by the Kaplan-Meier method and log-rank tests. Univariate and multivariate Cox-regression analyses were performed to determine the effects of probable prognostic factors including age, gender, ECOG score, histology, NLR, dNLR, PNI, CEA, ΔNLR, ΔdNLR, ΔPNI for OS. Hazard ratios and 95% confidence intervals (CIs) were estimated using Cox regression analysis. Statistical analysis was performed with SPSS software version 21 (SPSS IBM Corp., Armonk, NY, USA), and differences were considered statistically significant at p < 0.05.

Results

The median patient age was 61 (41–74) years, female/male ratio was 3/17, 12 (60%) had an ECOG PS of 0 or 1 and 17 (85%) of our patients were smokers. Thirteen patients (65%) had adenocarcinoma, one (5%) had squamous, two (10%) had large cell and four (20%) had more rare histological subtypes. Five (25%) of our patients had epidermal growth factor receptor (EGFR) mutations, six (30%) patients had no EGFR mutation and nine (45%) patients EGFR status was unknown. No patients had Anaplastic Lymphoma Kinase (ALK) mutation. Forty percent of the patients (n: 8) had been treated with ≥2 lines of therapy. The median number of nivolumab cycles was 15 (range, 1–88), 70% of patients (n: 14) had received more than six treatment cycles. Patient characteristics have been shown also shown in Table 1. The median follow-up duration was 9 (1–44) months, 17 patients had progressive disease, eight patients (40%) were alive at the 12th month of treatment and four (20%) were alive at the 36th month and study completion (44th month).

The relationship among OS and PFS and clinic-demographic variables has been shown in Table 1. The median OS was 7 months (mean: 14,8 months) and median PFS was 3 months

(mean: 10,7 months). OS and PFS were not significantly associated with sex, age (<65 vs. ≥65 years), histologic subtype (adenocarcinoma vs. another tumour subtype), and the number of treatment cycles before nivolumab treatment (1 vs. ≥2). Both median PFS (3 months) and OS (14 months) were longer in ECOG PS 0–1 patient than in ECOG PS 2 patients (1 and 2 months, p:0,006, p:0,000 respectively). Patients treated with ≥6 cycles of nivolumab had statistically longer median PFS and OS than in patients with <6 cycles of nivolumab (PFS: 3 vs. 1 month, p: 0,026, OS: 13 vs. 2 months, p: 0,000, respectively).

The median cut-off values were 2.9 (1.54–46.5), 1.95 (0.93–11.07), 35 (22-45), and 40.4 ng/mL (1.25–817) for NLR, dNLR, PNI and CEA levels, respectively. The median OS and PFS in patients with low NLR (<2.9, 14 months and 4 months) and high NLR (≥2.9, 4 months and 3 months) were significantly different (p: 0.015 and 0.025, respectively). OS was longer in cases with low dNLR (<1,9) than high dNLR (≥1.9) but PFS was not significant (OS: 14 vs 4 months, p:0,026, PFS: 3 vs 3 months, p:0,053). As shown in Table 1, PFS and OS were found to be significantly longer in patients with high PNI (≥35) than patients with low PNI (<35) (3 vs. 1 month, p:0,038, 12 vs. 3 months, p:0,009, respectively). On the other hand, patients with high CEA (≥40.4 ng/mL) had shorter PFS and OS than patients with lower CEA (<40.4 ng/mL) (2,4 vs. 19 months, p:0,038, 6,6 vs. 23 months, p:0,010, respectively).

When we evaluated changes in pre and post-treatment (after 3 cycles) NLR and dNLR were not significant for PFS (p: 0.565

and p: 0.213, respectively). OS was not found to be different according to the change in NLR (p: 0.903) but was significantly longer in the patients showing a decrease in dNLR after 3 cycles of nivolumab (21 vs. 6 months, p = 0.049). PNI increase after 3 cycles was found to be associated with longer PFS and OS (23,1 vs. 2,5 months, p:0,020, 27,6 vs 6,7 months, p:0,003, respectively) (Figure 1).

Prognostic significance of clinico-demographic characteristics and prognostic indicators including NLR, dNLR, PNI, CEA for OS is shown in Table 2. NLR, dNLR, PNI, CEA, and PNI changes (increase) have been found to be prognostic for OS in univariate analyses (p:0,023, p:0,035, p:0,016, p:0,018, p:0,007, respectively). However, in multivariate analysis, only change in PNI has been found to be an independent prognostic factor (HR: 0,153, %95 CL 0,37-0,631, p:0,009).

Discussion

Immunotherapy has been found to improve the survival of patients with metastatic NSCLC compared with conventional chemotherapy. However, data predicting response to ICIs are limited and impracticable [9]. In our study group, PFS and OS were found to be better in patients treated by nivolumab, in patients with good PS, treated more than six cycles and with low NLR, dNLR, CEA and high PNI reflecting systemic inflammation. An increase in PNI after three cycles compared with baseline was found to be significantly associated with longer OS and PFS and this finding was the only independent
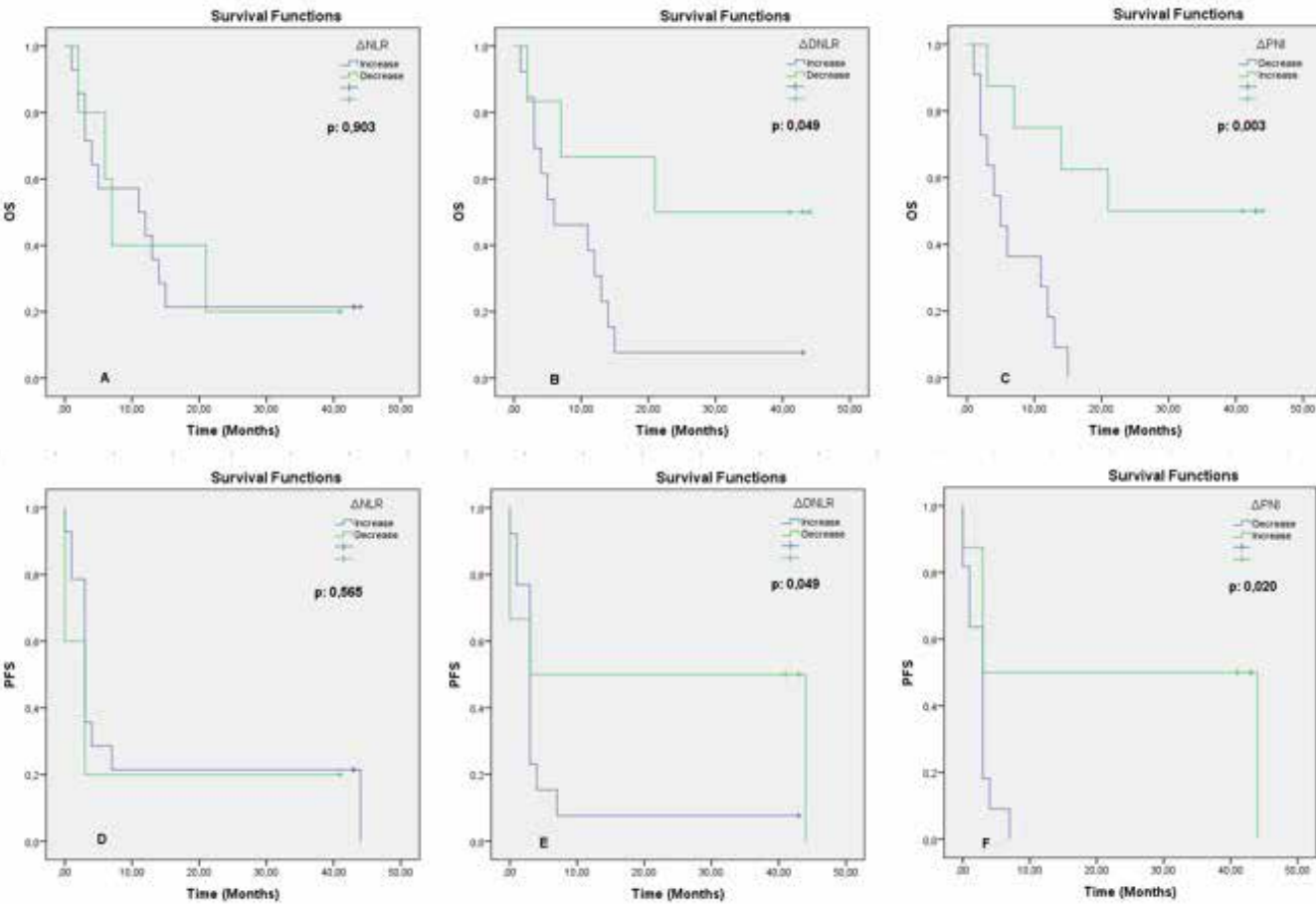

Figure 1. PFS and OS times according to dynamic inflammatory markers changings: ΔNLR (A-D), ΔDNLR (B-E), ΔPNI (C-F). ΔNLR: NLR change, ΔDNLR: DNLR change, ΔPNI: PNI change

risk factor for OS. For the first time in literature demonstration of the predictive value of dynamic PNI change in patients treated with nivolumab is important in addition to the already detected clinical and laboratory findings. It is considered that the combined evaluation of dynamic nutritional and immunological status reveals more valuable prognostic results than the evaluation of the basal inflammatory status in nivolumab treated patients.

There is continuous interaction between tumor and immune system. At the beginning, tumor cells are killed by the immune system (elimination) but in later times, tumor cells escape from immune system by using PD1/PDL1 and CTLA-4 pathways [10]. Nivolumab is IgG4 humanized monoclonal antibody and blocks PD-1 receptors. Firstly, nivolumab has been found to be more active than conventional antineoplastic drugs in metastatic NSCLC in the CheckMate 017 and CheckMate 057 trials and has been approved by the Food and Drug Administration in metastatic NSCLC [11-12]. Similar to the CheckMate studies, 40% of our patients were alive after 1 year of therapy, 20% of the patients were aliveafter 3 years of therapy (ChekMate 017/057 1- year survival rate 42%/51%, 3-year survival rate 16%/18%, respectively). Median OS and PFS have been found to be 11,1 (9,2-13,1) and 2,56 (2,2-3,4) months respectively in a 3-years follow up. In our study group, OS was shorter than in those studies due to poorer performance status of our cases: 40% of our patients had ECOG PS 2 while all the CheckMate patients had ECOG PS 0–1. This finding has been confirmed by Manrique et al; OS has been found as 2,3 months in cases with ECOG PS 2 while 11,7 months in cases with a performance score 0-1 [13]. No significant associations between PFS or OS and age, sex, histologic subtype, number of previous chemotherapy regimens or smoking status have been found in our study because of the small sample size.

It is very well known that tumor antigens activate neutrophils, lymphocytes, and natural killer cells and due to their role in inflammation, these cells are important components of tumorigenesis [14]. High NLR and dNLR are markers of systemic inflammation and independent predictors of survival in cancer patients [15-16]. The anti-tumour activity of ICIs depends on interaction with lymphocytes. Changes in NLR before and during treatment have been shown to be associated with the efficacy of immunotherapy in previous studies [17]. Low pre-treatment NLR or decrease after treatment have been found to improve response in cases treated with nivolumab by Ameratunga et al [18]. Change in NLR has been found as a marker of outcomes in NSCLC cases treated with PD-1 antibody by Suh et al [19]. High pre-treatment NLR and platelet-to-lymphocyte ratio have been found to be predictive for shorter OS and NLR values in weeks 2 and 4 of treatment and have been found to be predictive for response to nivolumab in cases with advanced NSCLC [20-21]. High dNLR at baseline has been found by Russo et al. to be associated with no response to nivolumab [22]. In our study, we found the prognostic significance of NLR and dNLR in NSCLC treated by ICIs and the predictive value of change in dNLR at 3th cycle of nivolumab. This is the first study showing shorter survival in cases with decreasing dNLR after 3 cycles of nivolumab treatment. However, ICIs comprise a dynamic

Table 1. Overall and progression-free survival, clinical characteristics and inflammatory markers in the 20 NSCLC patients.

	Total (n)	Total (%)	OS Mean	OS Median	OS p	PFS Mean	PFS Median	PFS p
Gender								
Female	3	15	15	13	0.871	4,3	3	0.962
Male	17	85	14,7	6		11,8	3	
Age (years)								
<65	14	70	15,1	7	0.852	11,6	3	0.348
≥65	6	30	13,5	2		8	1	
ECOG score								
0–1	12	60	22,9	14	0.000	16,7	3	0.006
2	8	40	2.6	2		1.6	1	
Histology								
Adenocarcinoma	13	65	15,8	11	0.702	12	3	0.409
Others	7	35	12,4	7		7,8	3	
Number of prior chemotherapies								
1	12	60	10,8	6	0.241	5,9	3	0.230
≥2	8	40	20,6	11		17,7	3	
Number of nivolumab cycles								
≥6	14	70	20,1	13	0.000	14,5	3	0.026
<6	6	30	2.3	2		1.7	1	
NLR								
<2.9	9	45	21,7	14	0.015	17,8	3	0.025
≥2.9	11	55	6.3	4		2	3	
DNLR								
<1.9	10	50	22,5	14	0.026	18,9	3	0.053
≥1.9	10	50	7.1	4		2.5	3	
PNI								
<35	7	35	4,9	12	0.009	2,1	1	0.038
≥35	13	65	20,2	3		15,3	3	
CEA								
<40.4 ng/mL	10	50	23	15	0.010	19	3	0.038
≥40.4 ng/mL	10	50	6,6	3		2.4	3	
ΔNLR								
Decrease	5	38.5	15,4	7	0.903	9,4	3	0.565
Increase	14	61.5	15,3	11		11,6	3	
ΔDNLR								
Decrease	6	46.2	27	21	0.049	22,5	3	0.213
Increase	13	53.8	10,1	6		5,9	3	
ΔPNI								
Decrease	11	57,8	6,7	5	0,003	2,5	3	0,020
Increase	8	42,2	27,6	21		23,1	3	
Overall	20	100	14,8	7		10,7	3	

ECOG: Eastern Cooperative Oncology Group, NLR: neutrophil–lymphocyte ratio, DNLR: derived neutrophil–lymphocyte ratio, PNI: Prognostic Nutritional Index, CEA: carcino-embryonic antigen, ΔNLR: NLR change, ΔDNLR: DNLR change, ΔPNI: PNI change

area in the treatment of NSCLC, and information at this era is increasing day by day. Simple variables like NLR and dNLR will be important in predicting and monitoring response to ICIs. PNI has been found to be prognostic in various types of

Table 2. Univariate and Multivariate Analysis of Potential Prognostic Factors for OS

OS	Univariate		Multivariate	
	HR (%95 CI)	P	HR (%95 CI)	P
Age (<65)	0,904 (0,310-2,636)	0,854	-	-
Gender (male)	1,109 (0,314-3,923)	0,872	-	-
ECOG score	429,2 (0,260-707912)	0,109	-	-
Histology	1,217 (0,439-3,369)	0,706	-	-
NLR	0,298 (0,105-0,843)	0,023	0,301 (0,085-1,066)	0,063
DNLR	0,322 (0,112-0,924)	0,035	0,916 (0,203-4,141)	0,909
PNI	4,0,32 (1,299-12,515)	0,016	1,945 (0,419-9,021)	0,396
CEA	4,233 (1,286-13,937)	0,018	-	-
ΔNLR	0,931 (0,295-2,943)	0,904	-	-
ΔDNLR	0,287 (0,077-1,073)	0,064	-	-
ΔPNI	0,160 (0,042-0,607)	0,007	0,153 (0,37-0,631)	0,009

ECOG: Eastern Cooperative Oncology Group, NLR: neutrophil–lymphocyte ratio, DNLR: derived neutrophil–lymphocyte ratio, PNI: Prognostic Nutritional Index, CEA: carcinoembryonic antigen, ΔNLR: NLR change, ΔDNLR: DNLR change, ΔPNI: PNI change

cancer and the main difference from other parameters is its reflection of the nutritional status of the patient in addition to inflammatory status [23]. Albumin as a negative acute phase reactant has been found to be decreased with increased inflammation and this is associated with poor prognosis in many cancer types. Cytokines released by inflammation causes to decrease in lymphocyte counts and anti-tumoral functions [24]. For these reasons, PNI is a good predictor of inflammation, poor nutritional status, and poor prognosis. The prognostic importance of PNI in cases treated by nivolumab is not surprise due to the effective function of ICIs on the lymphocytes. However, there is only one study showing the importance of PNI in cases treated by nivolumab. Nakao et al. have found that early discontinuation of the therapy and shorter PFS is associated with low PNI in cases treated by nivolumab [25]. We found shorter PFS and OS in cases with low PNI and this supportive for Nakao's study. Additionally, an increase in PNI after 3 cycles has been found to be an independent factor for OS both in univariate and multivariate analyses as the first time in our study. This finding suggests that not only inflammatory status but also nutritional status is important for prognosis and dynamic changes in PNI during treatment may be more predictive in cases on ICI treatment. For this reason, not only baseline markers but also the follow up of dynamic changes during treatment are important to determine which patients will be benefitted from ICIs and also to prevent side effects of ICI therapy. However, these findings need to be confirmed by other studies.

High CEA levels have been found to be associated with increased tumor burden and poor prognosis in lung cancer and in other cancers. Also, there are some studies showing the prognostic value of CEA level in NSCLC patients using nivolumab. An association between high CEA (≥13.8 ng/mL) and short PFS and decreased response to ICI treatment has been reported by Kataoka et al [26]. This is also confirmed in our study. The available evidence shows that low CEA predicts

improved outcomes and prognosis.

Due to the retrospective nature of the study and small number of patients, consideration of median values as cut off values should be confirmed by future prospective studies with larger patient populations.

Conclusion

Five year OS rate in advanced stage NSCLC is 1-2% while this rate is 15% in cases treated by ICIs but ICIs are expensive and may be toxic in some cases. For this reason, it is very important to use predictive markers for OS and response to ICI therapy and there are many ongoing studies examining these markers. We found longer PFS and OS in nivolumab treated cases with ECOG<2, low NLR, dNLR, CEA, and high PNI. Additionally, to the best of our knowledge, in this small study, we found the predictive value of increased PNI for OS both in univariate and multivariate analysis during nivolumab treatment. For this reason, dynamic follow up of PNI is predictive to select the patients benefitting from nivolumab and to determine the longer survivors.

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